AD_____

Award Number: DAMD17-02-1-0489

TITLE: Computer-Aided Interval Change Analysis of Microcalcifications on Mammograms for Breast Cancer Detection

PRINCIPAL INVESTIGATOR: Lubomir Hadjiiski, Ph.D.

CONTRACTING ORGANIZATION: University of Michigan
Ann Arbor, Michigan 48109-1274

REPORT DATE: July 2004

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	July 2004	Annual (1 Jul 03 - 30 Jun 04)

4. TITLE AND SUBTITLE
Computer-Aided Interval Change Analysis of Microcalcifications on Mammograms for Breast Cancer Detection

5. FUNDING NUMBERS
DAMD17-02-1-0489

6. AUTHOR(S)
Lubomir Hadjiiski, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Michigan
Ann Arbor, Michigan 48109-127

E-Mail: lhadjisk@umich.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES
Original contains color plates. All DTIC reproductions will be in black and white.

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

The goal of this project is to develop a computer-aided diagnosis (CAD) system for interval change analysis of lesions on mammograms. An important component of the CAD system is the multistage regional registration technique for identifying corresponding microcalcification clusters on temporal pairs of mammograms. In the first stage, an initial search region was estimated on the prior mammogram based on the cluster location on the current mammogram. In the second stage the search region was refined. In the third stage the cluster was detected within the search region. In the first stage we used the regional registration method (RRM), which outperformed the warping techniques. 175 temporal pairs of mammograms were used for evaluation. The average distance between the estimated and the true cluster centroids on the previous mammogram after the initial stage was 7.95±4.73mm. In the second stage, automated detection of microcalcification cluster within the search region is performed. Using our current cluster detection program with standard thresholds, 76.6% (134/175) TP with 0.45 false positives (FP) were detected within the search region. Using a high-sensitivity threshold, 89.1%(156/175) TP with 0.43 FP were detected. In the third stage the correspondence classifier was used and it reduced the FP rate to an average of 0.19 FP cluster with sensitivity of 81% (141/175).

14. SUBJECT TERMS
Breast Cancer, Computer-Aided Diagnosis, Screening, Classification, Image Analysis

15. NUMBER OF PAGES
15

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

(3) Table of Contents

(4) Introduction

Treatment of breast cancer at an early stage can significantly improve the survival rate of patients. Mammography is currently the most sensitive method for detecting early breast cancer, and it is also the most practical for screening. Although general rules for differentiation between malignant and benign lesions exist, in clinical practice, approximately only 15-30% of cases referred to surgical biopsy are actually malignant. A number of research groups are in the process of developing computer-aided diagnosis (CAD) methods which can provide a consistent and reproducible second opinion to the radiologist for the detection and classification of breast abnormalities.

Radiologists routinely compare mammograms from a current examination with those obtained in previous years, if available, for identifying interval changes, detecting potential abnormalities, and in evaluating breast lesions. It is widely accepted that interval changes in mammographic features are very useful for both detection and classification of abnormalities. However, CAD techniques that use multiple exams for detection or characterization have not been commonly explored, probably because of the difficulty in the registration of the compressed breast images from different exams. We have been investigating methods for analysis of temporal changes of masses on mammograms to improve detection and classification. To our knowledge, there is no existing CAD technique for registration of microcalcification clusters or classification of microcalcifications based on temporal change information.

The extraction of any meaningful information from a prior mammogram first requires a common frame of reference between the current and prior mammograms. Several complicating factors, such as breast compression difference between current and prior mammograms, energy difference between the two imaging conditions, differences in screen film properties and film processing conditions, and potential changes in breast structures between the two images with patient age, make it difficult to obtain such a frame of reference. On breast images, there are no invariant landmarks (except for the nipple) that can serve as control points in conventional image registration methods to register the two mammograms. In this project, we propose to develop an innovative regional registration method that does not depend on specific control points. We will first approximately align the current and prior mammogram based on maximization of mutual information. Next, we will design a novel approach in which the computer emulates the radiologists' search method in finding corresponding lesions on mammograms. Automated search of microcalcification cluster within the search region on the prior mammogram will be performed. Our current automated microcalcification detection algorithm will provide a basis for this search. However, since the detection is limited to the small search region, the detection can be performed in high resolution and the algorithm parameters can be adjusted to improve the detection sensitivity of the very subtle clusters on the prior mammograms without excessive trade-off in increasing false-positives. A correspondence classifier will be developed to identify the matched pair of clusters on the two mammograms. The image features of the corresponding microcalcification clusters can then be automatically extracted and feature measures characterizing interval changes derived. A classification scheme to differentiate malignant and benign clusters using the interval change information will be developed. This computerized interval change analysis will be an important component of a CAD system for mammographic interpretation.

This project aims at developing a novel interval change analysis scheme to improve the accuracy of CAD. We will investigate the problem of classifying microcalcifications as malignant or benign based on temporal changes in mammographic features using a combination

of computer vision, automated feature extraction, statistical classification, and artificial intelligence techniques. We hypothesize that the use of temporal information would improve the ability of CAD to offer an accurate and objective second opinion to radiologists which, in turn, would increase the positive predictive value of mammography, reduce the number of benign biopsies, and hence reduce both cost and patient morbidity. If integrated in a complete CAD system, the algorithms to be developed in this project may also increase the efficacy of mammography for early detection of breast cancer.

(5) Body

In the second year (7/1/03-6/30/04) of this grant, we have performed the following studies:

(A) Database collection of malignant and benign breast microcalcification cases that have multiple examinations (Task 1)

We continued collecting the data set for this study from the files of patients who had undergone biopsy at the University of Michigan. The mammograms are scanned and the images are saved in our storage device using automated graphic user interface developed in our laboratory. Additionally the film information is recorded in a Microsoft Access database. Temporal pairs of images were obtained. The current mammogram of each temporal pair exhibited a biopsy-proven mass. We scan both cranio-caudal (CC) and mediolateral-oblique (MLO) views. The mammograms were digitized with a LUMISCAN 85 laser scanner at a pixel resolution of 0.05 mm x 0.05 mm and with 12-bit resolution.

While the regional registration technique can be used for determining a corresponding structure or region for any structure (both normal tissues and masses) in the breast, in this study we are analyzing its accuracy on biopsy-proven masses alone. The location of the mass on the current mammogram is identified by an Mammography Quality Standards Act (MQSA)-approved radiologist experienced in breast imaging using an interactive image analysis tool on a UNIX workstation. To provide the ground truth for evaluation of the computerized method, the radiologist manually identifies the corresponding region on the previous mammogram. Bounding polygons enclosing the microcalcification cluster on the current mammogram and the corresponding object on the previous mammogram are provided by the radiologist for each case. Each microcalcification cluster as well as the corresponding structure on the previous mammogram are rated for its visibility on a scale of 1 to 10, where the rating of 1 corresponded to the most visible category. The size of the microcalcification cluster on the current mammogram as well as the size of the corresponding structure on the prior mammogram are also measured by the radiologist. The parenchymal density is rated based on the Breast Imaging Reporting and Data System (BI-RADS) lexicon.

(B) Development of a regional registration technique for localization of a search region for the corresponding microcalcification cluster on the prior mammogram of the same view. (Task 2)

We continued the development of a multistage regional registration technique for identifying corresponding microcalcification clusters on temporal pairs of mammograms. This detection approach mimics the method used by radiologists for searching corresponding lesions on mammograms, i.e., the lesion is searched at approximately the same radial distance from the nipple on both views, and feature comparison will be used for further identifying the matching lesion. In the first stage, an initial search region was estimated on the prior mammogram based on the lesion location on the current mammogram. In the second stage the search region was refined. In the third stage the lesion was detected within the search region.

Initially, the breast image was segmented from the background in the current and prior mammograms. We used the methods already developed in out lab, which work reliably for segmentation of the breast image from the background for our automated detection algorithms for single images [1], [2].

For the first stage of the multistage regional registration technique we need the nipple location on the current and prior mammograms. We are in the process of developing an

automated nipple detection program. Currently its accuracy is about 85% in a data set of 744 images (91% for 599 images with visible nipple and 62% for 145 images with invisible nipple) [3]. However, at this time we used manually marked nipple locations on the mammograms. We are still working to further improve the accuracy of the nipple detection algorithm aiming its use into the initial step of our automated interval change analysis scheme.

Initial global alignment of mammograms

In the first stage of registration, an initial fan-shaped search region is automatically defined on the prior mammogram based on the cluster location on the current mammogram. The cluster on the current mammogram can either be detected by an automated program or selected interactively by a radiologist. Currently we used the markings of the cluster locations given by the radiologist.

In this year of the project, for the initial estimation of the lesion centroid location on the prior mammogram we used our regional registration method (RRM) [4][5], based on the radial distance between the nipple and the lesion centroid and the angular distance between the nipple-lesion centroid axis and the breast boundary on the current mammogram. This selection was based on the results obtained during the first year of the project. At that time we compared RRM method, the linear (affine (AF)) and nonlinear (thin plate splines (TPS)) global warping of the current mammogram. The RRM method outperformed the warping techniques. It localized the corresponding lesions on temporal pairs of mammograms with the highest accuracy and the lowest standard deviation among the 5 methods. The results were presented at RSNA, 2003 [6].

In this year of the project, the increased data set of 175 temporal pairs of mammograms from 65 patients containing biopsy-proven microcalcification clusters was used. By using the RRM, the average distance between the estimated and the true centroid of the microcalcification clusters on the prior mammogram was 7.95 ± 4.73 mm.

We will continue our studies to improve the technique and evaluate its accuracy on a larger data set.

Definition of search region

An initial fan-shaped search region centered at the predicted location by RRM method from previous stage of the cluster centroid is then defined on the prior mammogram.

Using a search region with an average area of 1401 mm^2 allowed all clusters for the 175 pairs to be within the fan shape search region. That size of the search region was defined before from the mass local registration [5], which was large enough to include all of the clusters.

We still will continue to improve the registration methods in order to refine the localization and reduce the size of the search region. A search region with smaller size will contain less false clusters.

(C) Adaptation of the automated detection method for identification of candidates of microcalcification clusters within the search region. (Task 3)

We continued working on the adaptation of the automatic microcalcification detection for identification of mirocalcification clusters within a small search region. The search region (ROI) estimates the area that the cluster is most likely located but it does not provide the exact location. As the next step, automated detection of microcalcification cluster within the search region is

performed. Our current automated microcalcification detection algorithm [7] provides a basis for this search. Since the detection is limited to the small search region, the algorithm parameters can be adjusted to improve the detection sensitivity of the very subtle clusters on the prior mammograms without excessive trade-off in increasing false-positives (FPs).

In the second stage of the registration technique, we investigated the possibility of detection of cluster candidates within the search region with our automated cluster search program with increased sensitivity. We performed tuning of the cluster search program by adjusting the signal to noise threshold (SNR), minimum and maximum values for the number of detected signals, the neural network output threshold. We observed that with higher values for the minimum and maximum limits for the number of detected signals (i.e. allowing larger number of detected signals), and using higher neural network output threshold we obtained better sensitivity with smaller number of FP.

Using our conventional current cluster detection program with standard thresholds, 76.6% (134/175) of the clusters (TP) with an average of 0.45 false positives (FP) were detected within the search region on the prior mammogram.

Using a high-sensitivity threshold and parameters, the cluster search program detected 89.1% (156/175) of the true clusters (TP) with an average of 0.43 false positives (FP) cluster within the search region on the prior mammograms.

We are adapting the program to use 50 um images by retraining the parameters of the detection algorithm for 50 μm pixel size to optimize its accuracy. We are concentrating our efforts to improve the detection of the true individual microcalcifications without increasing the FP calcifications within the search area.

We will continue to investigate the possibilities to increase the sensitivity without increasing substantially the FP within the search region in order to detect more very subtle clusters.

(D) Feature extraction techniques and initial definition of similarity measure for matching corresponding microcalcification clusters on current and prior mammograms (Task 4)

The cluster (TP) on the current image was paired with every detected cluster (TP or FP) in the search region to form (TP-TP) and (TP-FP) pairs. Texture and morphological features were extracted from the clusters on the current and the prior mammograms. We extracted morphological features such as area, contrast, axis ratio and eccentricity of an effective ellipse, and moments of the individual microcalcifications and their statistics within a cluster such as the mean, standard deviation, or histogram shape (e.g., skewness and kurtosis). The extracted texture features were calculated from the spatial gray-level dependence (SGLD) matrices [8], and from the gray level difference statistics (GLDS) [9, 10]. These texture features describe characteristics such as contrast, local homogeneity, and regularity in the image.

Difference similarity measure was derived from the extracted features of the TP or FP clusters for each temporal pair. We formed the following similarity measures between the current and prior features for each individual feature: the difference, the absolute difference, the squared difference, and the Euclidean distance.

We compared the performance of above similarity measures for the design of the correspondence classifier which is reported in the next section.

We will continue the design of new types of features and similarity measures. We studied a number of similarity measures for the task of template matching of a template containing a current

lesion (current mammogram) within the search region on prior mammogram containing the prior lesion, which is closely related to correspondence classifier reduction of TP-FP pairs . We found that correlation, cosine and Gamma similarity measures outperformed similarity measures such as mutual information. The results of this study are accepted for publication in Medical Physics [11] and were presented at IWDM 2004 [12].

We will study how useful the correlation, cosine, and Gamma similarity measures, which showed a great promise for template matching, are going to be in the case of the correspondence classifier.

(E) Design of a correspondence classifier for identification of matched cluster pairs (Task 5)

In the final stage, a correspondence classifier was designed to reduce the false pairs (TP-FP) within the search region. We continued the design of a correspondence classifier. We used the above obtained difference similarity measure features as the input to the classifier.
A leave-one-case-out training and testing resampling scheme was used for feature selection and classification. A stepwise feature selection was used in order to obtain a subset of effective features. We used a linear discriminant classifier to merge the selected features for classification of the TP-TP and TP-FP cluster pairs.

The best result for the correspondence classifier was obtained for a combination of the squared difference morphological features and the squared difference of SGLD features. 11 features on average were selected. The test area under ROC curve Az, for the correspondence classifier was 0.76. The correspondence classifier reduced the FP rate to an average of 0.19 FP cluster with sensitivity of 81% (141/175). These results will be presented at the RSNA 2004 [13].

In the future year we will continue studying and developing different classifiers and ways to represent the correspondence information between prior and current TP and FP clusters.

(F) Initial development of feature measures and temporal classifier for characterization of temporal changes in microcalcification clusters. (Task 6)

In this study, a new classification scheme using interval change information was developed to classify mammographic microcalcification clusters as malignant and benign. In this preliminary study we used radiologist marked locations of the clusters as well as manually selected locations of the individual microcalcifications within the clusters for a subset of the entire dataset. As a first step in the design of the classifier of temporal microcalcification clusters, we were using that ideal situation in order to understand potential limits of the classification approach. Additionally, having manually marked individual microcalcifications makes possible to compare the quality of the automatic detection of microcalcifications.

From each cluster, 20 run length statistic texture features (RLSF) and 21 morphological features were extracted [14]. Twenty difference RLSF were obtained by subtracting a prior RLSF from the corresponding current RLSF. The feature space consisted of the current and the difference RLSF, as well as the current and the difference morphological features. The RLSF were extracted from radiologist's marked cluster locations. The morphological features were extracted from manually selected individual microcalcifications from the radiologist's selected clusters.

A linear discriminant analysis classifier (LDA) and stepwise feature selection were used to select the most useful feature subsets and to merge the features into a discriminant score. A leave-one-case-out resampling scheme was used to train and to test the LDA classifier. The classification accuracy was analyzed by receiver operating characteristic (ROC) methodology.

In this preliminary study, 65 temporal image pairs from 29 patients containing biopsy-proven microcalcification clusters on the current mammograms were chosen from patient files. Eleven of the cases were malignant and 18 were benign. Nineteen of the temporal pairs were malignant and 46 benign.

An average of 10 features were selected from the 29 training subsets. The selected features included 2 difference RLS features and 8 morphological features from the current image. The same two difference RLS features and six of the morphological features were consistently selected for almost all of the 29 training subsets. The remaining two morphological features varied depending on the data subsets. The classifier achieved an average training A_z of 0.97 and a test A_z of 0.85.

The difference RLS texture features and morphological features were useful for identification of malignancy in temporal pairs of mammograms. The information on the prior image improved characterization of the microcalcification clusters: 2 out of the 10 selected features contained prior information.

The ultimate goal of the project is to have an automatic CAD system for characterization of temporal cases on malignant and benign. For that purpose a feature extraction and classification should be carried out with the clusters and individual microcalcifications obtained automatically from the registration stage.

In the future year we will develop and compare classification approaches in order to classify the clusters on malignant and benign based on automatically detected clusters and individual microcalcifications.

(6) Key research accomplishments in current year as a result of this grant

- Increase of the temporal microcalcification database (collection of new temporal cases and extraction of regions of interest) (Task 1).
- Selection of RRM method for establishing corresponding locations in current and prior mammograms as most accurate compared to the linear and nonlinear warping methods (Task 2).
- Successful adaptation of the automated detection method for identification of candidates of microcalcification clusters within the search region to high sensitive mode (Task 3).
- Morphological and texture feature extraction and initial definition of difference similarity measures for matching corresponding microcalcification clusters on current and prior mammograms (Task 4).
- Design of a correspondence classifier for identification of matched cluster TP-TP pairs, that improved sensitivity and specificity of the cluster detection based on squared difference similarity measures (Task 5).
- Development of texture (RLS) and morphological feature measures for characterization of temporal changes in microcalcification clusters (Task 6).
- Development of the classifier for classification on malignant and benign clusters based on manually extracted clusters and individual microcalcifications (Task 6).

(7) Reportable Outcomes

Publications in current year as a result of this grant

[1] L. Hadjiiski, H.P. Chan, B. Sahiner, C Zhou, M.A. Helvie, M.A. Roubidoux, "Computerized Regional Registration of Corresponding Masses and Microcalcification Clusters on Temporal Pairs of Mammograms for Interval Change Analysis", *89th Scientific Assembly and Annual Meeting of the Radiological Society of North America (RSNA)*, Chicago, Illinois, 2003, pp. 389.

[2] Hadjiiski LM, HP Chan, B Sahiner, MA Helvie, MA Roubidoux, C Zhou, "Interval change analysis based on computerized regional registration of corresponding microcalcification clusters on temporal pairs of mammograms," To be presented at the *90th Scientific Assembly and Annual Meeting of the Radiological Society of North America*, Chicago, IL, Nov. 28-Dec 3, 2004.

Copies of publications are enclosed with this report.

(8) Conclusion

As a result of the support by the USAMRMC grant, in the second year of this project, we have (1) collected additional cases with temporal microcalcification clusters; (2) Applied the RRM for the localization of the search region for the corresponding microcalcification cluster on the prior mammogram; (3) Adapted the automated detection method for identification of candidates of microcalcification clusters within the search region; (4) Extracted texture and morphological features and defined difference similarity measures for matching corresponding microcalcification clusters on current and prior mammograms; (5) design a correspondence classifier for identification of matched cluster based on extracted features and the difference similarity measures; (6) develop feature measures and temporal classifier for characterization of temporal changes in microcalcification clusters.

The results obtained so far are encouraging. The RRM showed to be better for the localization of the search region than the linear and nonlinear warping methods. It allowed to have all the clusters within the search region on the prior mammogram. We were successful to adapt the automated microcalcification detection system to be more sensitive for identification of candidates of microcalcification clusters within the local search region. It was able to detect substantially more true clusters without increasing the FP rate compared to the conventional detection system. The squared difference similarity measure applied to the morphological features in combination with SGLD features was the successful combination for the input to the correspondence classifier. The correspondence classifier was able to reduce the TP-FP pairs resulting in less FP clusters within the search region on prior. The new classification scheme, using interval change information, to classify mammographic microcalcification clusters as malignant and benign showed promising results. Morphological and RLS features were useful for the classification.

The ultimate goal of the project is to have an automatic CAD system for characterization of temporal cases on malignant and benign. For that purpose in the feature year a feature extraction and classification will be carried out with the clusters and individual microcalcifications obtained automatically from the registration stage.

(9) References

1. Petrick N, Chan HP, Wei D, Sahiner B, Helvie MA and Adler DD, "Automated detection of breast masses on mammograms using adaptive contrast enhancement and texture classification," Med Phys 23, 1685-1696 (1996).
2. Zhou C, Chan H, Petrick N, Helvie M, Goodsitt M, Sahiner B and Hadjiiski L, "Computerized image analysis: Estimation of breast density on mammograms.," Med Phys.,28 (6), June (2001) pp. 1056-1069.
3. Zhou C, HP Chan, C Paramagul, MA Roubidoux, B Sahiner, LM Hadjiiski, N Petrick, "Computer-aided diagnosis on mammograms using multiple image analysis: computerized nipple identification," *Med Phys, (in press)* 2004.
4. S.S. Gopal, H.P. Chan, T.E. Wilson, M.A. Helvie, N. Petrick, B. Sahiner, "A regional registration technique for automated interval change analysis of breast lesions on mammograms", *Medical Physics,* 1999, 26:2669-2679.
5. L. Hadjiiski, H.P. Chan, B. Sahiner, N. Petrick, M. Helvie, "Automated Registration of Breast Lesions in Temporal Pairs of Mammograms for Interval Change Analysis – Local Affine Transformation for Improved Localization", *Medical Physics*, 28 (6), June 2001, pp. 1070-1079.
6. L. Hadjiiski, H.P. Chan, B. Sahiner, C Zhou, M.A. Helvie, M.A. Roubidoux, "Computerized Regional Registration of Corresponding Masses and Microcalcification Clusters on Temporal Pairs of Mammograms for Interval Change Analysis", *89th Scientific Assembly and Annual Meeting of the Radiological Society of North America (RSNA)*, Chicago, Illinois, 2003.
7. Chan HP, Lo SCB, Sahiner B, Lam KL and Helvie MA, "Computer-aided detection of mammographic microcalcifications: Pattern recognition with an artificial neural network," Med Phys 22, 1555-1567 (1995).
8. Haralick RM, Shanmugam K and Dinstein I, "Texture features for image classification," IEEE Trans Sys Man and Cybern SMC-3, 610-621 (1973).
9. Sahiner B, Chan HP, Petrick N, Wei D, Helvie MA, Adler DD and Goodsitt MM, "Classification of mass and normal breast tissue: A convolution neural network classifier with spatial domain and texture images," IEEE Trans Med Img 15, 598-610 (1996).
10. Weszka JS, Dyer CR and Rosenfeld A, "A comparative study of texture measures for terrain classification," IEEE Trans Sys Man and Cybern 6, 269-285 (1976).
11. Filev P, LM Hadjiiski, B Sahiner, H-P Chan, MA Helvie, "Comparison of similarity measures for the task of template matching of masses on serial mammograms," *Med Phys (accepted)* 2004.
12. Hadjiiski LM, B Sahiner, HP Chan, N Petrick, MA Helvie "Automated interval change analysis of masses in serial mammograms - evaluation of an adaptive similarity measure for

mass matching," *Proc. Digital Mammography IWDM 2004: 7th International Workshop on Digital Mammography* (in press).

13. Hadjiiski LM, HP Chan, B Sahiner, MA Helvie, MA Roubidoux, C Zhou, "Interval change analysis based on computerized regional registration of corresponding microcalcification clusters on temporal pairs of mammograms," To be presented at the *90th Scientific Assembly and Annual Meeting of the Radiological Society of North America*, Chicago, IL, Nov. 28-Dec 3, 2004.
14. L. Hadjiiski, H.P. Chan, M. Gurcan, B. Sahiner, N. Petrick, M.A. Helvie, M. Roubidoux "Computer-Aided Characterization of Malignant and Benign Microcalcification Clusters Based on the Analysis of Temporal Change of Mammographic Features", Presented at the *SPIE International Symposium on Medical Imaging*, San Diego, California, February 23-28, 2002. *Proc. SPIE Medical Imaging, 2002, 4684, pp.749-753.*

(10) Appendix

Copies of publications are enclosed with this report.

378 • 11:20 AM

Computerized Regional Registration of Corresponding Masses and Microcalcification Clusters on Temporal Pairs of Mammograms for Interval Change Analysis

L.M. Hadjiiski, PhD, Ann Arbor, MI • H. Chan, PhD • B. Sahiner, PhD • C. Zhou, PhD • M.A. Helvie, MD • M.A. Roubidoux, MD (lhadjisk@umich.edu)

PURPOSE: To develop a registration technique for automated identification of corresponding lesions on a temporal pair of mammograms of the same view. This technique is the basis for interval change analysis of breast lesions in CAD applications.

METHOD AND MATERIALS: A multi-stage registration technique is being developed. In the first stage, an initial search region was estimated on the prior mammogram based on the lesion location on the current mammogram. In the second stage the search region was refined. In the third stage the lesion was detected within the search region. For the initial estimation of the lesion centroid location on the prior mammogram, we previously developed a regional registration method (RRM), based on the radial distance between the nipple and the lesion centroid and the angular distance between the nipple-lesion centroid axis and the breast boundary on the current mammogram. In the present study, we compared the RRM to the use of warping techniques for the initial estimation of the lesion location. The current mammogram was warped by affine (AF) or thin plate splines (TPS) transformation in combination with simplex optimization in order to maximize a similarity measure between the breast areas on the current and prior mammograms. Correlation and mutual information (MI) similarity measures were evaluated. A set of 390 temporal pairs of mammograms containing biopsy-proven masses or microcalcification clusters was used. The true lesion locations were identified by an MQSA radiologist on all mammograms. 72 temporal pairs were used for training the parameters of the warping techniques. The remaining 318 pairs were used for testing the performance of the 5 methods. The registration accuracy was analyzed by evaluating the average distance between the centroids of the estimated and the true lesion locations on the prior mammogram.

RESULTS: The average distance between the estimated and the true lesion centroids on the previous mammogram after the initial stage was: RRM = 8.5±6.2mm, correlation-AF = 9.0±6.7 mm, correlation-TPS = 10.3±8.2 mm, MI-AF = 9.2±7.5 mm, MI-TPS = 9.5±8.6 mm. After the final

registration stage, the average distance between the estimated and the true centroids was: RRM=6.4±8.9mm, correlation-AF = 7.0±9.5 mm, correlation-TPS = 7.4±10.2 mm, MI-AF = 6.9±9.5 mm, MI-TPS = 7.2±11.1 mm.
CONCLUSIONS: The RRM method outperformed the warping techniques. It localized the corresponding lesions on temporal pairs of mammograms with the highest accuracy and the lowest standard deviation among the 5 methods.

To be presented at the *90th Scientific Assembly and Annual Meeting of the Radiological Society of North America*, Chicago, IL, Nov. 28-Dec 3, 2004.

Interval Change Analysis based on Computerized Regional Registration of Corresponding Microcalcification Clusters on Temporal Pairs of Mammograms

Lubomir Hadjiiski, Heang-Ping Chan, Berkman Sahiner, Mark A. Helvie, Marilyn Roubidoux, Chuan Zhou

PURPOSE: To develop an automated method for characterization of microcalcification clusters using interval change information on serial mammograms. This analysis will be useful for identification of new or growing clusters in a detection system or for classification of malignant and benign clusters in a diagnostic system.

MATERIALS AND METHODS: The automated interval change analysis method consisted of two stages: (1) detection of corresponding cluster on the prior, and (2) classification of cluster as new, growing, or stable. In the first stage, based on the position of a detected cluster on the current mammogram a regional registration procedure identified the local area that might contain the corresponding cluster on the prior. A search program was used to detect cluster candidates within the local area. The cluster on the current mammogram was then paired with the detected candidates to form (TP-TP) and (TP-FP) pairs. Features were automatically extracted and a correspondence classifier was designed to reduce the false pairs (TP-FP). In the second stage, the current cluster is classified as new if no cluster is detected in prior, or the detected clusters will be classified as growing or stable based on analysis of the current and prior pairs. In this study, we focussed on the first stage. 175 serial mammogram pairs containing biopsy-proven clusters on current mammograms were used. An MQSA radiologist identified the corresponding clusters on the mammograms. On priors, the radiologist rated 12 of the 175 clusters as not visible and the subtlety of 18 clusters as 9 and 10 on a scale of 10. A leave-one-case-out resampling scheme was used for feature selection and classification.

RESULTS: The search program detected 89% (156/175) of the clusters with an average of 0.43 FP cluster on priors. The correspondence classifier identified 81% (141/175) of the TP-TP pairs with 21 false matches within the 162 image pairs that had detected clusters.

CONCLUSIONS: Our study demonstrated that our registration and matching technique can find the corresponding cluster on the prior with high sensitivity, considering many of the clusters were very subtle. This is a promising step for automated analysis of clusters on serial mammograms.